INTRODUCTION

AN ACTION PLAN FOR LIVER DISEASE RESEARCH

This trans-NIH Action Plan for Liver Disease Research was developed to respond to the need to advance research on liver and biliary diseases with the ultimate aim of decreasing the burden of these diseases in the United States. Biliary disease was included in this Action Plan because of the interrelatedness of the liver and biliary tree, the shared nature of their diseases, and the overlap in research goals. The focus of this Action Plan is on identifying areas of scientific opportunity to serve as a stimulus to progress and to help direct NIH research resources toward practical but important goals in the prevention and control of liver and biliary diseases.

Liver and biliary diseases affect Americans of all ages and walks of life. At present, an estimated 5.5 million Americans (approximately 2 to 3 percent of adults) have chronic liver disease or cirrhosis, and more than 20 million (approximately 12 percent of adults) have gallbladder disease. The combined diagnoses of chronic liver disease, cirrhosis, viral hepatitis, and liver cancer make liver disease one of the 10 leading causes of death in the United States. Death rates from some forms of liver disease are decreasing while rates of others, such as viral hepatitis and liver cancer, are on the rise, both in the United States and worldwide. While difficult to approximate, an estimated one quarter of Americans will suffer from a liver or biliary disease at some point during their lifetime.

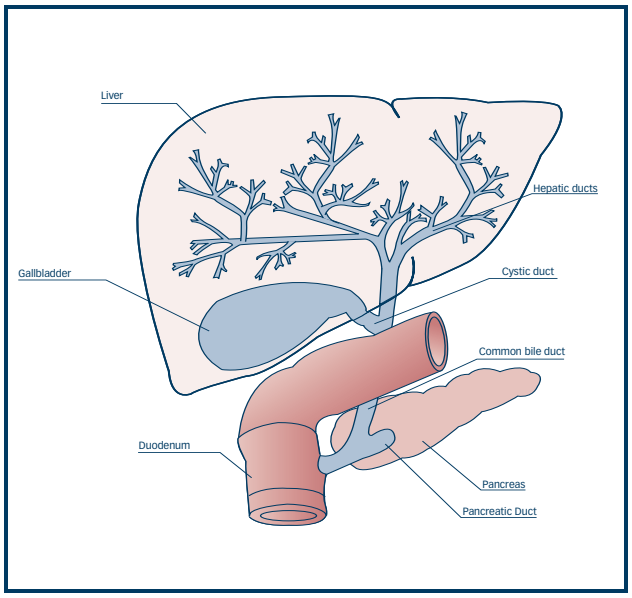
The current burden of liver and biliary diseases calls for greater efforts in their prevention and control. Progress in controlling liver and biliary diseases depends largely on advances in understanding of these diseases through biomedical research. Indeed, the advances that have occurred in controlling liver and biliary diseases in the last ten to twenty years have arisen largely from research in areas such as liver transplantation, vaccine development against hepatitis A and B, elimination of post-transfusion hepatitis C, therapy of chronic viral hepatitis, prevention of acetaminophen-induced liver failure, as well as identifying the causes of Wilson disease, hemochromatosis, Alagille syndrome, and alpha-1-antitrypsin deficiency. Further advances in management of liver disease are now within reach, particularly with

the dramatic breakthroughs that have occurred in basic biology, fueled by remarkable new advances in genetics, molecular biology, mammalian and non-mammalian model systems, and the completion of the Human Genome Project. These advances have occurred as a result of public funding through the National Institutes of Health (NIH) and other Federal agencies, as well as from private funding through research foundations and industry. To gain greater control over liver and biliary diseases as health problems, further basic and clinical research is warranted that addresses fundamental issues in liver biology as well as translates new findings into specific means to diagnose, prevent, and treat liver diseases.

NIH-supported research activities in the next decade are expected to continue to yield breakthroughs toward reducing the burden of liver and biliary diseases. To realize this goal, careful assessment of research opportunities; coordination among NIH components, Federal agencies, and other organizations; and planning for the optimal use of future investments are all essential.

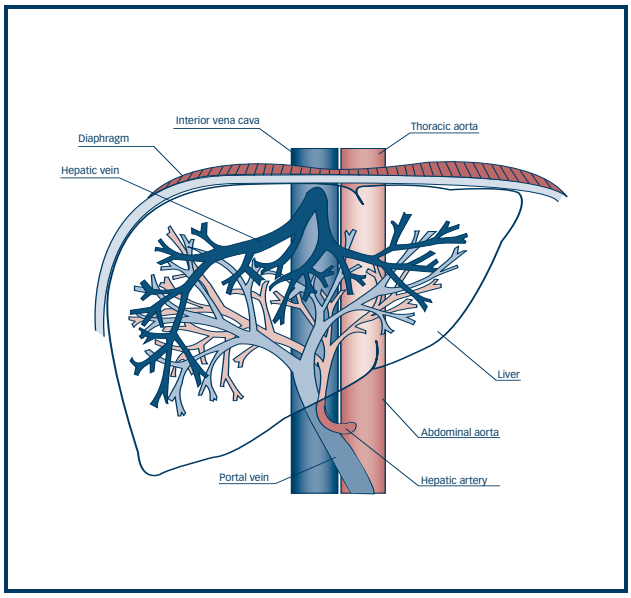
Figure 1. Basic Anatomy of the Liver and Biliary Tree

A. Anatomy of the Liver and Biliary Tree



The liver occupies the entire right upper quadrant of the abdomen. The liver, gallbladder, pancreas, and duodenum (upper small intestine) are connected by ducts, which allow these structures to coordinate bile formation and secretion. Disease can arise in these structures due to infection, genetic mutation, and/or exposure to toxic levels of alcohol, chemicals, or drugs. Adapted with permission from the National Digestive Diseases Information Clearinghouse, NIDDK.

B. Blood Supply of the Liver



The liver is supplied with blood carrying nutrients from the small intestine via the portal vein, as well as blood carrying oxygen from the heart via the hepatic artery. Blood from both these sources mixes in specialized capillaries called sinusoids, which contact the liver cells and provide them with nutrients and oxygen. After these substances have been extracted by the cells, the blood flows out of the liver through the hepatic vein and returns to the heart. Chronic liver disease can cause high blood pressure (portal hypertension), which leads to a host of medical complications. Adapted with permission from *The Merck Manual of Medical Information—Second Home Edition*, p. 807, edited by Mark H. Beers. Copyright 2003 by Merck & Co., Inc., Whitehouse Station, NJ.

LIVER DISEASE: OVERVIEW AND CURRENT BURDEN

OVERVIEW OF DISEASES OF THE LIVER AND BILIARY TRACT

Liver and biliary diseases can result from a variety of causes, including infectious agents, inherited defects, metabolic disturbances, alcohol, and toxins found in the environment, diet, or medicine cabinet. These diseases can be acute or chronic—acute indicating a sudden and transient illness or infection, and chronic indicating a more gradual, but persistent course. The most common forms of liver disease are acute and chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune liver conditions, metabolic liver diseases, and drug-induced liver injury. The most common causes of biliary disease are gallstones, autoimmune damage, and strictures. Chronic liver disease is the most common cause of liver cancer in the world, and gallstones and chronic biliary diseases are important causes of gallbladder and biliary tract cancers.

The most important consequences of acute liver and biliary diseases are the clinical symptoms of illness usually marked by jaundice (yellowish tinge to the skin and whites of the eyes), abdominal pain, nausea, poor appetite, and fatigue. Occasionally, acute liver injury leads to liver failure and death. Acute liver failure is the outcome of about 1 percent of cases of acute viral hepatitis and up to 10 percent of cases of acute drug-induced liver disease.

The most important consequence of chronic liver disease is the development of cirrhosis and portal hypertension. Cirrhosis is characterized by the progressive destruction of liver cells combined with abnormal regeneration and the accumulation of scar tissue, which also alters the blood flow through the liver and impairs functioning. Cirrhosis can develop as a result of any chronic liver disease, with the most common causes being hepatitis C and B, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and the autoimmune liver diseases – primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Once cirrhosis is present, a cascade of complicating conditions can develop, largely as a result of portal hypertension, defined by increased blood pressure in the portal vein that carries blood to the liver. Portal hypertension can then lead to esophageal varices (dilated veins in the lower esophagus that are subject to hemorrhage); hepatic encephalopathy (dysfunction of the brain or nervous system as a result of liver disease); ascites (fluid buildup in the abdominal cavity); and kidney failure. Cirrhosis also predisposes patients to develop hepatocellular carcinoma, the most common type of liver cancer. Although cirrhosis has, historically, been considered irreversible, recent data suggest that cirrhosis can be arrested and reversed to some extent by therapies for liver disease, particularly if treatment is initiated at an early or "incomplete" stage of cirrhosis. Ultimately, however, cirrhosis predisposes to liver failure and is the major reason for liver transplantation.

CURRENT BURDEN IN THE UNITED STATES

The impact of liver and biliary diseases on the U.S. population is considerable, whether viewed in terms of the number of individuals affected; the severity of the disease and its frequency of fatality; economic costs to the U.S. health care system; as well as those disease outcomes that are less readily quantifiable, but are important on a personal scale, such as disability and quality of life.

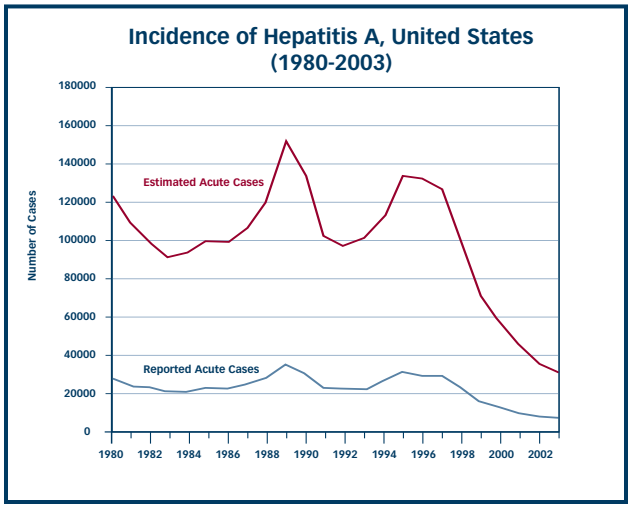
Prevalence and Incidence of Liver and Biliary Diseases

Liver and biliary diseases are common causes of morbidity and mortality in the United States. The frequency of these diseases is usually expressed as prevalence, which is defined as the number of individuals in the population who have the disease at any one time, or as incidence, which is defined as the number who develop the disease over a specific period, usually one year. Another very important way of expressing the frequency of the disease is as life-time likelihood of developing the disease, although this can only be estimated from incidence and prevalence data on a disease.

Viral Hepatitis: The most common causes of both acute and chronic liver disease are the various forms of viral hepatitis. Five viruses (hepatitis A, B, C, D, and E) have been identified as causing hepatitis in humans. The viruses that cause hepatitis A and B are now well characterized and have been grown in cell culture, and vaccines are now available to prevent their transmission. During the last decade, the incidence of new cases of hepatitis A and B in the United States has fallen significantly (Figure 2). In contrast, the virus that causes hepatitis C has yet to be grown in cell culture and has eluded attempts at vaccination. Although the incidence of new cases of hepatitis C is decreasing, the prevalence of chronic hepatitis C is high, and this disease is now the most common cause of chronic liver disease and need for liver transplantation in the United States.

Figure 2. Incidence of Hepatitis A and B in the United States: 1980-2003

Data used with permission from the Centers for Disease Control and Prevention.



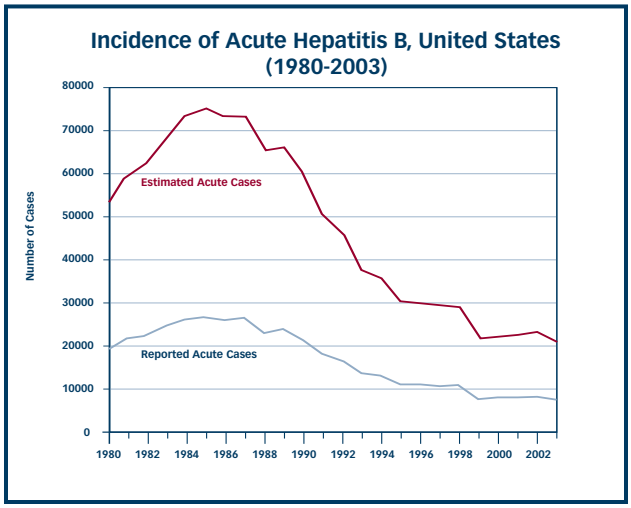


Table 1. Disease Burden from Hepatitis A, B and C in the United States (2003)

	Hepatitis A	Hepatitis B	Hepatitis C
Reported Numbers of Acute Cases	7,653	7,526	Not Available
Estimated Numbers of Acute Cases	33,000	21,000	4,900
Estimated Numbers of New Acute Infections	61,000	73,000	30,000
Estimated Number of Persons with Chronic Infection	None	1.25 million	2.7 million
Estimated Number of Deaths from Chronic Infection	None	5,000	8,000-10,000
Percent Ever Infected (Antibody Positive)	33.0%	4.9%	1.8%

Data used with permission from the Centers for Disease Control and Prevention.

In 2003, there were an estimated 61,000 new HAV infections (incidence rate of 21 per 100,000 population); 73,000 new HBV infections (incidence rate of 25 per 100,000 population); and 30,000 new HCV infections (incidence rate of 10 per 100,000 population) in the United States (Table 1). *Acute* hepatitis A accounted for 37 percent, hepatitis B for 45 percent, and hepatitis C for 18 percent of viral hepatitis cases; hepatitis D and E, being uncommon and somewhat difficult to diagnose, are rarely reported. The overall incidence of *chronic* viral hepatitis is not well defined, but recent surveys suggest that 45 new cases are diagnosed each year per 100,000 population. The majority of newly-diagnosed cases of chronic viral hepatitis are due to hepatitis C and most are not of recent onset, but, rather, are the result of recent discovery and diagnosis due to the fact that onset of chronic hepatitis is often silent and the resultant disease remains undetected for years.

A more accurate reflection of the burden of chronic viral hepatitis is the prevalence of these diseases. From serologic surveys done on the non-institutionalized civilian U.S. population, it is estimated that 1.25 million adult Americans have chronic hepatitis B, and 2.7 million have chronic hepatitis C. However, these are probably underestimates because the population-based surveys did not capture some high-risk populations, such as the homeless, persons in institutions, prisoners, and recent immigrants from areas of the world where chronic hepatitis is more common.

The overall prevalence and life-time risk for acquiring viral hepatitis are not well defined. As many as 33 percent of Americans will acquire hepatitis A infection at some time during life; 5 percent hepatitis B; and 1 to 2 percent hepatitis C (Table 1). In most instances, hepatitis A and B are silent, self-limited infections, with perhaps only one third of persons developing symptoms and jaundice. Hepatitis A does not lead to chronic infection, and hepatitis B results in chronic hepatitis in less than 5 percent of cases in adults. In contrast, hepatitis C, while frequently silent, leads to chronic infection in the majority of patients (70 percent). Rarely, hepatitis A and B can cause acute liver failure and death, but hepatitis C almost never results in these outcomes. In summary, at present about one third of Americans acquire a hepatitis virus infection (usually hepatitis A) sometime during life, and 2 percent of adults currently suffer from chronic viral hepatitis.

Alcoholic Liver Disease: Alcohol is a well known and common cause of liver disease. Generally, the liver is damaged only by heavy and prolonged alcohol use. Nevertheless, of the roughly 7 percent of Americans who abuse alcohol or are alcohol-dependent, only a minority develop liver injury. Alcohol causes accumulation of fat in the liver followed by injury, inflammation, and fibrosis. Alcoholic cirrhosis accounts for nearly half of deaths from chronic liver disease, and alcoholic liver disease is believed to affect approximately 1 percent of the adult population. Women are generally more susceptible to liver damage due to alcohol than men. Abstinence usually leads to improvement and even resolution of alcoholic liver disease, but it must be instituted early before there is advanced cirrhosis. Alcoholic liver disease is the cause of 8 percent of newly diagnosed cases of chronic liver disease, and the combination of alcoholic liver disease and hepatitis C accounts for another 22 percent of cases.

Nonalcoholic Fatty Liver Disease: Interestingly, a proportion of persons who appear to have alcoholic liver disease by blood tests and liver biopsy drink little or no alcohol. This finding led to the description of nonalcoholic steatohepatitis or NASH, a liver disease that is marked by the accumulation of fat in the liver accompanied by liver cell injury, inflammation, and fibrosis in patients who drink little or no alcohol. NASH typically occurs in middle-aged persons who are overweight, obese, and/or have type 2 diabetes. However, in recent years, NASH has also been found to occur in young persons, even children, and in individuals who are not overweight and do not have diabetes. NASH has been shown to be a common cause of liver disease, accounting for approximately 10 percent of all newly diagnosed cases of chronic liver disease and affecting approximately 2 percent of the adult population. Indeed, fatty liver without apparent liver injury is even more common, affects as much as 20 percent of the adult U.S. population, and is strongly associated with obesity and diabetes.

Gallstones: Gallstones are very common in the U.S. population. From cross-sectional surveys, it is estimated that 20 million adult Americans have gallstones or have had surgery to remove them (cholecystectomy). The prevalence of gallstones increases with age, and gallstones are more common in persons who are overweight or obese. The age-standardized prevalence rates for gallstone disease in the United States are 5 to 9 percent for adult men and 14 to 27 percent for adult women, depending upon race and ethnicity. Gallstones are particularly common among Hispanic American women and American Indians. Indeed, in some American Indian populations, over 64 percent of adult women have gallstone disease.

Drug-induced Liver Disease: Medications, including prescription drugs, over-the-counter agents, and complementary and alternative medicines, are important causes of acute liver disease. The incidence and prevalence of drug-induced liver disease are not known, but many commonly used medications are associated with a 1 to 3 percent incidence of some degree of liver injury (as indicated by elevations in serum aminotransferase levels) during the first 1 to 6 months of chronic use. Liver injury from medications tends to be short-lived and mild. More severe cases with jaundice and significant liver injury are relatively uncommon, occurring in fewer than 1 percent of individuals. Of course, medications that cause liver injury more frequently are not generally approved for use, and, indeed, drug-induced liver injury is the most common reason for not bringing a drug to market or for FDA withdrawal of an approved medication.

Autoimmune Liver Diseases: Most other causes of liver disease are uncommon, but they seriously affect the health of the afflicted person. Autoimmune liver diseases include autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis. These chronic liver diseases can lead to end-stage liver disease, generally over a period of 10 to 30 years.

Table 2. Indications and Diagnosis of Adult Patients Undergoing Liver Transplantation in the United States (2003)

Diagnosis	Number	Percent of Total
Chronic Hepatitis C	1,484	29%
Chronic Hepatitis B	145	2.8%
Alcoholic Liver Disease *	830	16.2%
Cryptogenic Cirrhosis	435	8.5%
Hepatocellular Carcinoma	398	7.8%
Sclerosing Cholangitis	299	5.8%
Primary Biliary Cirrhosis	209	4.1%
Autoimmune Hepatitis	148	2.9%
Acute Liver Failure	318	6.2%
Other	858	16.7%
Total	5,124	

* 26% of cases of alcoholic cirrhosis undergoing transplant were also infected with hepatitis C virus.

Data used with permission from the Scientific Registry of Transplant Recipients.

The estimated prevalence of autoimmune liver diseases ranges from 10 to 40 per 100,000 population.

Cancers of the Liver and Biliary Tree: These cancers have long been considered to be uncommon or rare in the U.S. population. Unfortunately, this observation is no longer correct. Both hepatocellular carcinoma (the most common form of primary liver cancer) and cholangiocarcinoma (the most common form of cancer of the biliary tract) are increasing in incidence in the United States, while the frequencies of most other forms of cancer are decreasing. Hepatocellular carcinoma has nearly doubled in incidence in the past 20 years and now ranks 8th as a cause of cancer deaths in males in the United States. Most cases of hepatocellular carcinoma occur in patients with an underlying chronic liver disease accompanied by cirrhosis. Thus, liver cancer can be considered a complication of chronic liver disease rather than a cancer unrelated to liver disease.

Special Populations: Liver and biliary diseases can strike across age and racial/ethnic groups, genders, and socioeconomic classes. However, the risk of contracting liver and biliary diseases is disproportionately higher in certain groups, particularly in lower socioeconomic groups and disadvantaged persons. The frequency of liver disease also varies greatly among different racial and ethnic groups. Liver disease is more common in Hispanic whites and African Americans than in non-Hispanic whites.

Liver disease is not common in childhood, but the liver diseases that do occur tend to be severe and cause a life-long burden of illness. Neonatal severe liver disease occurs in approximately 1 in 2,500 live births. The main causes of neonatal liver disease are biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis, and alpha-1-antitrypsin deficiency liver disease.

Table 3. Indications and Diagnosis of Pediatric Patients Undergoing Liver Transplantation in the United States (2003)

Diagnosis	Number	Percent of Total
Biliary Atresia	187	34%
Alagille Syndrome	11	2%
Acute Liver Failure	66	12%
Cryptogenic Cirrhosis	14	2.6%
Sclerosing Cholangitis	6	1%
Autoimmune Hepatitis	18	3%
TPN-Induced Liver Disease	41	7.5%
Hepatoblastoma	11	2%
Wilson Disease	7	1%
Metabolic Liver Disease	29	5%
Other	156	29%
Total	546	

Data used with permission from the Scientific Registry of Transplant Recipients.

Liver Transplantation: Liver transplantation is the only therapy of lasting benefit for end-stage liver disease and cirrhosis and can be life-saving in cases of acute liver failure. Temporal trends on liver transplantation and the etiology of liver disease provide further insights into the prevalence and relative importance of liver diseases.

At present, more than 5,000 liver transplants are performed in adults and more than 500 in children in the United States each year at approximately 120 specialized medical centers. Most liver transplants are done using livers from deceased donors. However, 12 percent of pediatric transplants and 5 percent of adult transplants are done using living donor livers. The use of living donors for liver transplantation continues to be controversial, largely because of the risk of the operation to the healthy donor.

The major reason for liver transplantation in adults is end-stage liver disease and cirrhosis (Table 2). Chronic hepatitis C is the major reason listed, accounting as a single diagnosis for approximately 30 percent of transplants, but also contributing to a proportion of the 8 percent of transplants done for hepatocellular carcinoma and the 16 percent of transplants done for alcoholic liver disease. Other important causes of liver transplantation include primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, and hepatitis B. A proportion of patients undergoing liver transplantation have end-stage liver disease of unknown cause and are given the diagnosis of "cryptogenic" cirrhosis. Many of these cases appear to be attributable to NASH, which becomes difficult to diagnose once advanced cirrhosis is present. Hepatocellular carcinoma is becoming a major reason for liver transplant, originally accounting for only 2 to 3 percent of transplants

in the 1990s, but now accounting for transplant in 8 percent of cases. This increase is largely attributable to changes in the allocation system for transplantation that have allowed for accelerated transplantation for small cancers. Importantly, the cause of hepatocellular carcinoma is usually a chronic liver disease, and a great proportion of these cancers are a consequence of hepatitis C, alcoholic liver disease, and hepatitis B.

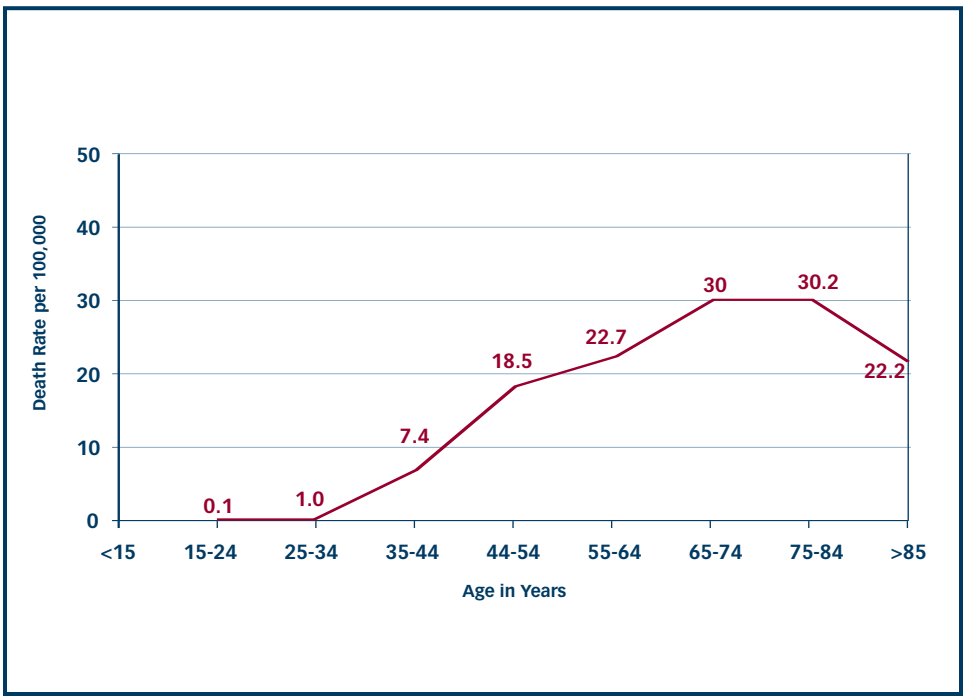
Acute liver failure is the reason for approximately 8 percent of transplants in adults and 12 percent in children. Of importance, the major cause for acute liver failure in adults is drug-induced liver disease while the major cause of this syndrome in children is unknown or "cryptogenic."

In children, the major indication for liver transplantation is biliary atresia, accounting for at least one third of cases (Table 3). Other major reasons for transplantation in pediatric age groups are acute liver failure, total parenteral nutrition-induced liver disease, metabolic liver diseases, alpha-1-antitrypsin deficiency, hepatoblastoma, and autoimmune hepatitis.

Mortality from Liver and Biliary Diseases

The number of deaths due to liver and biliary diseases has been difficult to accurately assess due to such difficulties as inaccurate information in death certificates, under-reporting of liver disease, and problems with interpreting the current system used to code diseases. Chronic liver disease and cirrhosis is currently considered the 12th leading cause of death in the United States. The age-adjusted death rate for chronic liver disease and cirrhosis is now 9.5 per 100,000 population, which is the lowest rate in U.S. history. However, the current data likely underestimate mortality from chronic liver disease due to under-reporting, as well

Figure 3. Death Rates in the United States from Liver Disease by Age in 2001



Data from the National Center for Health Statistics, Centers for Disease Control and Prevention. September 18, 2003. *National Vital Statistics Reports* 52(13): 28.

Table 4. Twelve Leading Causes of Death in the United States in 2001 by Age Group

	Age Group										
Rank	**<1**	**1-4**	**5-9**	**10-14**	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65+**	**All Ages**
1	Congenital Anomalies 5,513	Unintentional Injury 1,714	Unintentional Injury 1,283	Unintentional Injury 1,553	Unintentional Injury 14,411	Unintentional Injury 11,839	Malignant Neoplasms 16,569	Malignant Neoplasms 49,562	Malignant Neoplasms 90,223	Heart Disease 582,730	Heart Disease 700,142
2	Short Gestation 4,410	Congenital Anomalies 557	Malignant Neoplasms 493	Malignant Neoplasms 515	Homicide 5,297	Homicide 5,204	Unintentional Injury 15,945	Heart Disease 36,399	Heart Disease 62,486	Malignant Neoplasms 390,214	Malignant Neoplasms 553,768
3	SIDS 2,234	Malignant Neoplasms 420	Congenital Anomalies 182	Suicide 272	Suicide 3,971	Suicide 5,070	Heart Disease 13,326	Unintentional Injury 13,344	Chronic Low. Respiratory Disease 11,166	Cerebro-vascular 144,486	Cerebro-vascular 163,538
4	Maternal Pregnancy Comp. 1,499	Homicide 415	Homicide 137	Congenital Anomalies 194	Malignant Neoplasms 1,704	Malignant Neoplasms 3,994	Suicide 6,635	**Liver Disease 7,259**	Cerebro-vascular 9,608	Chronic Low. Respiratory Disease 106,904	Chronic Low. Respiratory Disease 123,013
5	Placenta Cord Membranes 1,018	Heart Disease 225	Heart Disease 98	Homicide 189	Heart Disease 999	Heart Disease 3,160	HIV 5,867	Suicide 5,942	Diabetes Mellitus 9,570	Influenza & Pneumonia 55,518	Unintentional Injury 101,537
6	Respiratory Distress 1,011	Influenza & Pneumonia 112	Benign Neoplasms 52	Heart Disease 174	Congenital Anomalies 505	HIV 2,101	Homicide 4,268	Cerebro-vascular 5,910	Unintentional Injury 7,658	Diabetes Mellitus 53,707	Diabetes Mellitus 71,372
7	Unintentional Injury 976	Septicemia 108	Influenza & Pneumonia 46	Chronic Low. Respiratory Disease 62	HIV 225	Cerebro-vascular 601	**Liver Disease 3,336**	Diabetes Mellitus 5,343	**Liver Disease 5,750**	Alzheimer's Disease 53,245	Influenza & Pneumonia 62,034
8	Bacterial Sepsis 696	Perinatal Period 72	Chronic Low. Respiratory Disease 42	Benign Neoplasms 53	Cerebro-vascular 196	Diabetes Mellitus 595	Cerebro-vascular 2,491	HIV 4,120	Suicide 3,317	Nephritis 33,121	Alzheimer's Disease 53,852
9	Circulatory System Disease 622	Benign Neoplasms 58	Cerebro-vascular 38	Influenza & Pneumonia 46	Influenza & Pneumonia 181	Congenital Anomalies 458	Diabetes Mellitus 1,958	Chronic Low. Respiratory Disease 3,324	Nephritis 3,284	Unintentional Injury 32,694	Nephritis 39,480
10	Intrauterine Hypoxia 534	Cerebro-vascular 54	Septicemia 29	Cerebro-vascular 42	Chronic Low. Respiratory Disease 171	**Liver Disease 387**	Influenza & Pneumonia 983	Homicide 2,467	Septicemia 3,111	Septicemia 25,418	Septicemia 32,238
11	Atelectasis 501	Chronic Low. Respiratory Disease 43	Anemias 25	Septicemia 40	Diabetes Mellitus 151	Influenza & Pneumonia 339	Chronic Low. Respiratory Disease 969	**Viral Hepatitis 2,060**	Influenza & Pneumonia 2,704	Hypertension 16,397	Suicide 30,622
12	Neonatal Hemorrhage 453	Meningitis 26	Perinatal Period 22	Diabetes Mellitus 32	Septicemia 133	Chronic Low. Respiratory Disease 290	Septicemia 829	Septicemia 1,977	Hypertension 1,462	Parkinson's Disease 16,181	**Liver Disease 27,035**

Data from the Vital Statistics System, National Center for Health Statistics, Centers for Disease Control and Prevention.

as exclusion of important chronic liver disease-related causes of death, such as viral hepatitis and conditions that occur as a result of chronic liver disease (i.e., sequelae such as liver cancer or complications such as esophageal hemorrhage or hepatic encephalopathy). In a recent analysis of trends in chronic liver disease mortality in the United States, the inclusion of viral hepatitis and sequelae of chronic liver disease including liver cancer in estimates of deaths from chronic liver disease showed that deaths did not decline in the 1990s as was previously thought. Use of this more inclusive definition for chronic liver disease places liver disease within the 10 leading causes of death in the United States, and could improve the accuracy of future estimates of chronic liver disease mortality, particularly as hepatitis C-virus related mortality has risen in recent years and may increase as much as 2-3 fold in the decades ahead.

For example, in the most recent overall mortality data from 2002, chronic liver disease and cirrhosis accounted for 27,045 deaths (1.1 percent of total deaths), but another 5,706 deaths were attributed to viral hepatitis; 14,046 to malignant neoplasms of the liver and intrahepatic bile ducts; and 2,965 to gallstones and other gallbladder diseases, totaling approximately 50,000 deaths per year (2 percent of all deaths). Retrospective surveys of death records also suggest that these liver diseases are underreported and that overall death rates from liver disease may be 30 percent higher than is estimated by the Centers for Disease Control and Prevention (CDC) based upon coding of death certificates.

Mortality from chronic liver disease varies greatly by age and gender. Thus, death from liver disease is higher in men than women. Most notably, however, chronic liver disease and cirrhosis combined is a frequent cause of death in Americans in the most productive years of life (Table 4). Thus, liver disease is the 4th leading cause of death in the United States in adults between the ages of 45 and 54 years. The incidence of liver disease increases with age, peaking in the 50s and 60s, and remaining stable or declining with more advanced age, when mortality from conditions such as heart disease, stroke, diabetes, cancer, and kidney disease rises precipitously (Figure 3). These observations indicate that liver disease is not an inevitable consequence of aging.

Liver disease also varies in frequency in different ethnic and racial groups. Mortality from chronic liver disease and cirrhosis is twice as high in American Indians and Hispanic whites than in other racial and ethnic groups in the United States. In American Indians between the ages of 35 to 44 years, liver disease is the second leading cause of death and accounts for 12 percent of deaths.

Liver disease has recently been found to be an increasingly common cause of morbidity and mortality in persons infected with the human immunodeficiency virus (HIV). Case series from several groups in the United States have reported that, since the introduction of highly active antiretroviral therapy to treat HIV infection, liver disease has become a major cause of death. HIV-infected persons are susceptible to a variety of liver diseases, including hepatitis B and C, NASH, alcoholic liver disease, and drug-induced liver injury. Hepatitis C appears to be the major cause of liver-related deaths in this patient population. Importantly, deaths from liver disease in HIV-infected persons are coded as related to HIV rather than as liver disease. These factors contribute to the under-reporting of liver disease as a cause of death on death records.

In conclusion, mortality studies illustrate several important issues regarding liver disease. First, liver diseases are heterogeneous and are difficult to classify together as a single cause of death. Second, liver disease is unique among several types of chronic disease in that the major burden of liver disease strikes those individuals in the most productive periods of adulthood. Finally, liver disease rates vary greatly among different socioeconomic and racial/ethnic groups. Thus, liver

and biliary diseases represent a major burden on the health of Americans that is not adequately reflected in overall mortality figures. When one then considers that most liver diseases are potentially preventable or treatable, these facts underscore how further advances in knowledge about liver diseases are likely to result in a material decrease in the burden of these diseases in the United States.

Economic Costs to the U.S. Health Care System

An important measure of the burden of disease is the economic cost. Chronic liver disease and cirrhosis is one of the most expensive digestive diseases in terms of health care costs, including costs of days of work lost of $222 million, and total costs of approximately $1.6 billion annually. Contributing to these costs is the care required for common complications of chronic liver disease, including portal hypertension, ascites, hepatic encephalopathy, and jaundice. Costs of care for chronic hepatitis C, which are estimated at $700 million annually, include the combined antiviral therapy necessary to suppress viral levels, as well as liver transplantation, which is often required by these patients. These HCV-related health costs are predicted to rise in future decades as morbidity and mortality increase, by some forecasts to anywhere between $6.5 and $13.6 billion annually. Liver cancer leads to direct costs of $1.3 billion each year. As cases of liver cancer increase and liver transplantation is used more frequently, these costs are likely to rise. Furthermore, cost estimates on liver disease and cancer do not include the economic costs of years-of-productive-life lost.

Gallbladder disease is one of the most prevalent and costly diseases. Of all the digestive diseases, gallbladder disease is the single most important and common diagnosis requiring hospital admission. Because of its frequency and the expense of cholecystectomy, gallbladder disease is estimated to result in total annual costs of $6 billion.

Quality of Life

Liver and biliary diseases have an impact on the personal lives of patients, in terms of their abilities to work and engage in social activities, their physical and emotional well-being, and their overall quality of life. Many liver diseases are silent, causing few, if any, symptoms despite ongoing injury that can lead to cirrhosis. Once cirrhosis is present, however, symptoms usually become prominent. The major symptoms of liver disease are fatigue, muscle weakness, nausea, poor appetite and weight loss, fluid retention, predisposition to bleeding and infection, depression, anxiety, and inability to work. Itching is a common symptom in patients with primary biliary cirrhosis, but it can arise in any form of liver disease and can be disabling. The overall rate of disability from liver disease in the population is not well defined. In a survey conducted in the 1980s, an estimated 112,000 people were disabled due to chronic liver disease or cirrhosis, and 48,000 due to gallstones. In World Health Organization estimates, cirrhosis accounts for a loss of approximately 14 million disability-adjusted life years worldwide, which is a measure of all the years of disability and lost life across the population due to the disease. Similarly, liver cancer is estimated to cause loss of 7 million disability-adjusted life years.

Importantly, the quality of life of patients with liver disease has been shown to improve significantly with effective therapies. Patients with chronic hepatitis C experience an improved quality of life if they have a sustained viral response to interferon therapy. Liver transplantation has been shown to dramatically improve the quality of life of patients with end-stage liver disease, in terms of physical and psychological well-being, as well as social functioning. Indeed, in some patients, quality of life after liver transplantation returns to the age- and sex-matched population norm.

LIVER DISEASE RESEARCH

ADVANCES AND OPPORTUNITIES

Significant progress has been made in several areas of research into understanding liver and biliary function and disease, as well as improving disease management and control to the benefit of patients and the general public. These advances have taken place as part of basic research in the laboratory on animal or cell models; in a clinical or public health research setting; and through efforts to bridge these realms, particularly in terms of the clinical application of knowledge gained through basic research (translation).

For example, basic research on hepatitis A and B led to the development of vaccines for both diseases, and subsequent public health programs defined their usefulness and led to a decrease in these diseases in the general population. Similarly, basic research on hepatitis B and C led to the development of tests to detect these viruses in blood, and, subsequently, blood banking policies led to screening of blood for these two agents, resulting in the virtual disappearance of post-transfusion hepatitis. Other advances have led to improvements in therapy of liver diseases, such as the introduction of interferon and ribavirin for treatment of hepatitis C. Patients with liver cancer have benefited from the development of methods to accurately image the tumor and treat it in a localized manner that is less invasive and more effective. Endoscopic and laparoscopic techniques have facilitated diagnosis and treatment of gallstones. Progress has been made in understanding the causes and processes of several forms of liver disease, including identifying the genetic defects responsible for inherited liver diseases, as well as in appreciating the ability of the liver to heal itself through regeneration. The development of liver transplantation through basic research, use of animal models, and, ultimately, clinical research in patients has transformed management of liver disease, offering a chance of survival for patients with end-stage cirrhosis. More recently, the development and refinement of living donor and split- or reduced-size liver transplantation procedures have been helpful in alleviating the shortage of liver organs and have had major effects on survival of children with advanced liver disease. Elaboration on these examples and other important research advances is presented in the "Recent Research Advances" sections of chapters in this Action Plan.

Building on these past gains, opportunities now exist to further advance research on liver and biliary diseases through NIH support and to translate new findings on disease pathways into new means of treating liver and biliary diseases and alleviating patient suffering. This Action Plan identifies areas of scientific opportunity that would be beneficial to pursue over the next decade within available resources of NIH support in order to advance knowledge and care of liver and biliary diseases. These opportunities are identified as "research goals" within each chapter of this Action Plan.

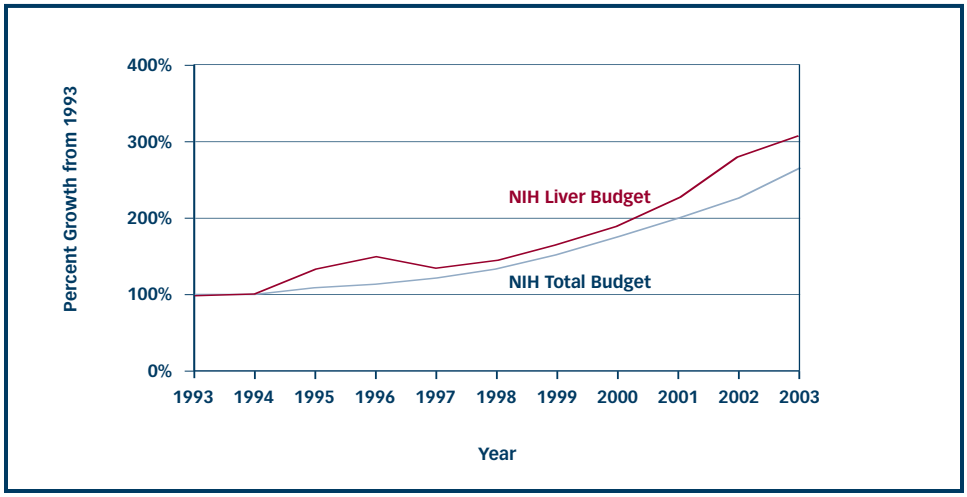
Table 5. NIH Expenditures for Liver Disease Research (FY 2003)

NIH Institute, Center, or Office*	Dollars
NIDDK	152,000,000
NIAID	69,661,000
NCI	63,701,000
NIAAA	34,491,000
NIEHS	25,189,000
NCRR	14,292,000
NHLBI	13,084,000
NICHD	3,740,000
NHGRI	3,201,000
NIDA	2,582,000
NIA	1,861,000
NCCAM	1,036,000
NINR	956,000
OD	820,000
FIC	730,000
NIDCR	555,000
NIMH	317,000
NCMHD	50,000
Total NIH	**388,266,000**

* See Appendix C for list of acronyms.

Data from NIH Office of Budget.

Figure 4. Growth in Liver Disease Research Funding by the NIH: 1993-2003



Data from NIH Office of Budget.

OVERVIEW OF CURRENT NIH FUNDING OF LIVER DISEASE RESEARCH

Many of the advances in liver and biliary research highlighted in this Action Plan were enabled in large part by vigorous NIH support in recent years. Within the NIH, 18 Institutes, Centers, and Offices currently support and collaborate on liver and biliary disease research with a total investment of $388 million in fiscal year 2003 (Table 5). This investment is the result of a 3-fold increase in research funding within the past decade (Figure 4). Importantly, during the period when the total NIH budget doubled (1998-2003), funding for liver and biliary disease research more than matched this pace of growth.

The majority of this liver disease research support is contributed by five Institutes:

- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, 39 percent),
- National Institute of Allergy and Infectious Diseases (NIAID, 18 percent),
- National Cancer Institute (NCI, 16 percent),
- National Institute on Alcohol Abuse and Alcoholism (NIAAA, 9 percent), and
- National Institute of Environmental Health Sciences (NIEHS, 6 percent).

Other Institutes, Centers, and Offices at the NIH that support liver and biliary disease research include:

- National Center for Research Resources (NCRR),
- National Heart, Lung, and Blood Institute (NHLBI),
- National Institute of Child Health and Human Development (NICHD),
- National Human Genome Research Institute (NHGRI),
- National Institute on Drug Abuse (NIDA),
- National Institute on Aging (NIA),
- National Center for Complementary and Alternative Medicine (NCCAM),
- National Institute of Nursing Research (NINR),
- Office of the Director (OD),
- Fogarty International Center (FIC),
- National Institute of Dental and Craniofacial Research (NIDCR),
- National Institute of Mental Health (NIMH), and
- National Center on Minority Health and Health Disparities (NCMHD).

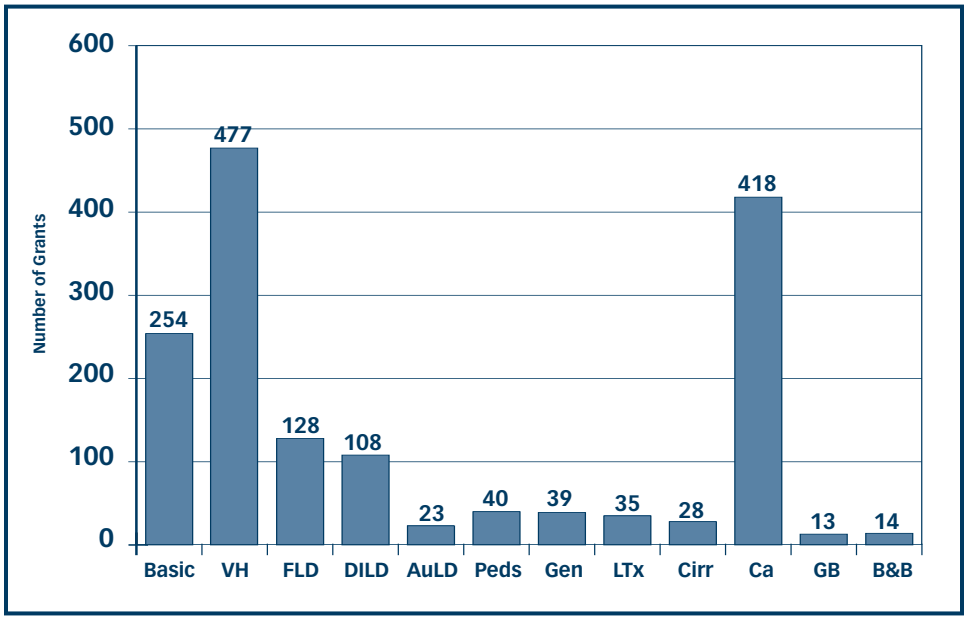
Liver disease-related research supported by the NIH includes studies of the liver and biliary system, under normal and disease conditions, and in basic and clinical research settings. NIH support for liver and biliary research is provided in the form of grants, awards, contracts, and fellowships awarded to extramural researchers and institutions for research and training, as well as support of intramural research projects. Most NIH-supported research is investigator-initiated, meaning that unsolicited grants were deemed of sufficient scientific merit through a process of peer review.

As part of developing this Action Plan, the grants in the entire NIH portfolio of liver disease research for the most recent fiscal year (FY 2002) were classified into one of 16 categories of liver research that parallel the chapters of this Action Plan. To perform this analysis, a single code was used to categorize grants, although many grants were relevant to more than one of the topic areas. This provided an overview of the current distribution of support among these different topic areas (Figure 5) by Institute. The major areas of NIH support were in basic research, viral hepatitis, and liver cancer. Fatty liver disease and drug- and toxicant-induced liver injury also received extensive support. Support of viral hepatitis research was shared among several Institutes, including the NIAID, NCI, NIDDK, NIAAA, NIDA, NHLBI, and NCRR. The majority of grants in liver cancer were funded by the NCI; in fatty liver disease by the NIAAA; and in drug- and toxicant-induced liver injury by the NIEHS. The NIDDK funded the majority of research on pediatric liver disease,

genetic liver disease, liver transplantation, complications of cirrhosis, and gallstones. In FY 2002, viral hepatitis was the subject of the most NIH grants in liver disease research, including those focusing on hepatitis B, hepatitis C, and HIV coinfection.

In addition to its direct support of liver and biliary research, the NIH has played an important role in bringing together the external clinical liver disease community to conduct critical reviews of recent developments in liver and biliary disease management through conferences and workshops. For example, in 2002, the NIH convened a Consensus Development Conference on the Management of Hepatitis C, which resulted in a published statement on current knowledge in this area. Other liver disease research meetings have convened on the topics of Management of Hepatocellular Carcinoma (April 2004); Management of Hepatitis C in Prisons (January 2003); Hepatitis C in African Americans (December 1999); Hepatitis C and Renal Disease (October 2003); Development of RNA Interference (RNAi) as an Antiviral Therapeutic to Fight Hepatitis C Virus Infection (September 2004); Management of Hepatitis B (September 2000); Role of S-Adenosyl-L-Methionine in the Treatment of Alcoholic Liver Disease (September 2001); Role of Iron in Alcoholic Liver Disease (October 2002); Role of Fatty Liver, Dietary Fat, and Obesity in the Progression of Alcoholic Liver Disease (October 2003); Complementary and Alternative Medications in Chronic Liver Disease (August 1999); Research Directions in Endoscopic Retrograde Cholangiopancreatography (January 2002); Future Directions in Research on Primary Biliary Cirrhosis (June 2003); Nonalcoholic Steatohepatitis (December 1998); and Drug Induced Liver Injury (October 2000). These conferences and meetings are supported by multiple NIH components, as well as other Federal agencies such as the Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), the U.S. Department of Veterans Affairs (VA), and the Agency for Healthcare Research and Quality (AHRQ), and, therefore, also serve to enhance coordination of liver disease research efforts across the NIH and the Federal government.

Figure 5. Sixteen Areas of Liver Research Grants Supported by NIH (FY 2002)



Basic=Basic research (Chapters 1-4, including Cell and Molecular Biology, 79 grants; Liver Injury, Inflammation, Repair, and Fibrosis, 36 grants; Developmental Biology and Regeneration, 61 grants; B=Bile, Bilirubin, and Cholestasis, 33 grants), VH = Viral hepatitis (Chapters 5 and 6, including HIV-related Viral Hepatitis, 52 grants), FLD = Fatty liver disease (Chapter 7), DILD = Drug-induced liver disease (Chapter 9), AuLD = Autoimmune liver disease (Chapter 9), Peds = Pediatric liver disease (Chapter 10); Gen = Genetic liver disease (Chapter 11), LTx = Liver transplantation (Chapter 12), Cirr = Cirrhosis and Complications of Liver Disease (Chapter 13); Ca = Liver cancer (Chapter 14), GB = Gallbladder disease (Chapter 15), B&B= Bioimaging and biotechnology (Chapter 16). Data from NIH Institute and Center budget offices.

ACTION PLAN

DEVELOPMENT AND ORGANIZATION

Initiation of the Planning Process and Enhanced Research Coordination

The Action Plan for Liver Disease Research originated with a letter sent to Elias Zerhouni, M.D., NIH Director, in Fall 2002, by Congressman Michael Bilirakis, Chair of the Subcommittee on Health of the Energy and Commerce Committee of the House of Representatives, which inquired about the status of liver disease research at the NIH and potential means to further focus efforts on combating this problem in the United States through NIH-supported research. Dr. Zerhouni responded with plans to build on the robust NIH liver disease research portfolio through various means to bring greater focus and coordination to liver disease research supported by the NIH. Of prime importance for the immediate future was the development of a trans-NIH Action Plan for Liver Disease Research, which would be developed under the auspices of a newly formed, NIH-wide coordinating committee focused on liver disease research. The coordinating committee was to be formed as a component of the existing, statutory Digestive Diseases Interagency Coordinating Committee (DDICC). The DDICC was established in 1985 through an amendment to the Public Health Service Act (Title 42 USC Section 285c-3) to promote collaboration among relevant Federal health agencies in order to provide a coordinated research effort to combat digestive diseases. Also, a new Liver Disease Research Branch was to be formed within the NIDDK, with an eminent liver disease research expert appointed as Chief, who would chair the liver disease research coordinating committee and lead the development of the Action Plan.

The implementation of these plans to spur liver disease research efforts supported by the NIH was initiated by Allen Spiegel, M.D., NIDDK Director, in July 2003, with the official establishment of the Liver Disease Research Branch (LDRB) within the Division of Digestive Diseases and Nutrition (DDDN) of the NIDDK, and the appointment of Jay H. Hoofnagle, M.D., an internationally recognized authority in liver disease and former director of the DDDN, NIDDK, as Chief of this Branch. The Liver Disease Research Branch also included Leonard Seeff, M.D., Special Expert on Viral Hepatitis; Jose Serrano, M.D., Director for the Liver and Biliary Program; and Edward Doo, M.D., Program Director of Liver Diseases Research. Dr. Hoofnagle and the LDRB staff then pursued the formation of the Liver Disease Subcommittee within the DDICC, with representation by 17 Institutes and Centers at the NIH that support liver and biliary research, which held its inaugural meeting in October 2003. The purpose of the Liver Disease Subcommittee, DDICC was to coordinate liver and biliary research efforts across the NIH, with its first charge in this vein being the development of this trans-NIH Action Plan for Liver Disease Research.

An Iterative Planning Process to Enable Broad Input

The Action Plan was developed through an open and inclusive planning process, with oversight by the Liver Disease Subcommittee, DDICC and leadership by the NIDDK Liver Disease Research Branch. It represents the contributions of a diverse and talented group of individuals who are committed to advancing liver disease research, including those from the NIH and other Federal agencies, intramural and extramural researchers, physicians, and representatives of professional and patient advocacy groups.

An open meeting was held in November 2003 attended by intramural and extramural researchers, clinicians, and representatives of professional and patient advocacy organizations to discuss how the Action Plan should be developed, including the nomination of Working Group members. Approximately 120 individuals, mostly liver disease researchers, physicians, and lay advocates from outside the NIH whose areas of expertise matched the broad range of topic areas addressed in this Action Plan, participated in the 16 Working Groups—one per topic area in this Action Plan—to provide input and comments by teleconference and email (See Appendix A. Part 2. for list of Working Group members). Each of these Working Groups was facilitated by a Working Group chairperson. First drafts of the chapters were then prepared by staff of the NIDDK Liver Disease Research Branch and distributed to the Working Groups for review and comments. After incorporation of these comments, second drafts were then sent to 16 separate groups of Primary Reviewers, with similar composition to the Working Groups; approximately 80 individuals participated as primary reviewers of the Action Plan content (See Appendix A. Part 2. for list of Primary Reviewers). Reviewer comments were incorporated by NIDDK Liver Disease Research Branch staff (third draft), and chapter drafts were posted on the Action Plan website *(http://liverplan.niddk.nih.gov)* for a month-long period of public comment (fourth draft). Members of the Liver Disease Subcommittee, DDICC, with significant assistance from major scientific and advocacy organizations such as the American Association for the Study of Liver Diseases (AASLD) and the American Liver Foundation (ALF), broadcasted the invitation for comment to all stakeholders who had not already participated in the Action Plan process, including members of the general public, government, academic institutions, professional societies, advocacy organizations, and industry. Following the incorporation of these comments, this final draft of the Action Plan was prepared.

Organization of the Action Plan for Liver Disease Research

For the purpose of structuring the Action Plan for Liver Disease Research, liver and biliary research was divided into 16 topic areas. The 16 chapters in this Action Plan are dedicated to addressing these topic areas. Each chapter is divided into the following sections:

- *Introduction and Background:* An overview of the area, including current understanding of biological and molecular processes, common conditions, disease burden, epidemiology, pathogenesis and natural history, as well as means of control, cure, and/or prevention.
- *Recent Research Advances:* An overview of the evolution of understanding and control of the disease and milestones in research, particularly in the previous 5-10 years.
- *Research Goals:* A summary of the research goals identified by the Working Group, which expands upon concepts related to goals listed in the Matrix of Research Goals. Each research goal is bulleted, and includes mention of any related goals in other chapters through cross-referencing (e.g., "see also Chapter 16, A1").
- *Steps to Achieve Research Goals:* A description of the major steps to enable advancement of

knowledge in this area of research, focusing on specific breakthroughs that would help to achieve the goals outlined in this area.

- *Matrix of Research Goals:* A 3-by-3-cell matrix with research goals in this area categorized as being short- (0-3 years), intermediate- (4-6 years), or long-term (7-10 years), and as being low-, medium-, or high-risk, in terms of degree of difficulty (Figure 6). The format of this matrix was modeled after one used by Elias Zerhouni, M.D., NIH Director, to set research goals for the NIH under the Government Performance and Results Act.

In the concluding sections of this Action Plan, a summary is presented of major cross-cutting research goals identified through the planning process that can be used in the monitoring and ultimate assessment of the Action Plan over the next decade.

GUIDING PRINCIPLES

The Action Plan for Liver Disease Research was intended to be a succinct, direct, and unbiased set of recommendations for ways of advancing knowledge about the liver and liver diseases through future NIH-supported research that is ultimately directed toward decreasing the burden of liver disease in the United States. The central focus of the Action Plan was to provide a series of achievable goals for liver disease-related research. These included both primary goals that would directly affect patients with liver disease, as well as secondary goals that would materially advance knowledge necessary to achieve the primary goals of decreasing the burden of liver disease.

Several principles guided the development of the Action Plan for Liver Disease Research. These principles are axiomatic, but have been found to be reliable in guiding initiatives in biomedical research. These principles are to:

- **Stress basic research.** Important, fundamental advances in management and prevention of liver disease will come primarily from fundamental advances in knowledge of liver function and liver diseases.

- **Strive to rapidly translate findings from *basic* research to practical means of diagnosis, prevention, treatment and cure of liver diseases.** Findings from basic research should be applied to clinical issues (bench-to-bedside research) in a timely, reasoned, efficient, and effective manner. The great increase in knowledge in biology and

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Figure 6. Matrix of Research Goals

	Short term (1-3 yrs)	Medium term (4-6 yrs)	Long term (7-10 yrs)
High risk (difficult)	A3	B3	C3
Intermediate risk	A2	B2	C2
Low risk (easy)	A1	B1	C1

Mission Statement

The goal of the Action Plan for Liver Disease Research is to advance research on liver and biliary diseases, with the aim of decreasing the burden of liver and biliary diseases in the United States.

medicine triggered by advances in cell and molecular biology, genetics, genomics, and the Human Genome Project needs to be applied to diagnosis, prevention, treatment, and cure of human diseases. Translation is a major component of the NIH Roadmap *(http://nihroadmap.nih.gov)* and is also a central focus of this Action Plan.

- **Strive to rapidly translate findings from *clinical* research to important directions for basic research.** Translational research is bidirectional. For example, findings in clinical investigation and clinical trials often provide new insights that need to be further pursued by basic, laboratory research. Thus, it is important to provide means of interaction between clinical and basic researchers to focus and refocus research efforts on important issues of liver disease prevention and management. The success of bidirectional translational research would be aided by the formulation of multidisciplinary research teams and productive communication, involvement, and interactions between clinical and basic researchers.

- **Strive to use the full potential of recent breakthroughs in research.** For example, research should capitalize on the wealth of molecular biologic information and tools stemming from such endeavors as the Human Genome Project and the Human Proteome Project and the advances in biotechnology and methodology in biomedical research.

Mission of the Action Plan for Liver Disease Research

To fulfill the mission of this Action Plan requires the efforts not only of the NIH to advance knowledge of liver and biliary diseases, but also the involvement and collaboration of all Federal, academic, professional, and advocacy partners committed to this mission, including those individuals and organizations involved in the development of this Action Plan. The combined efforts of these entities is required to support such activities as the development of population-based surveys of prevalence, guidelines for clinical practice, and educational and outreach programs for clinicians and patients.

Therefore, while the goals and recommendations described in this Action Plan apply specifically to NIH-supported research efforts, it is hoped that they may also serve to highlight opportunities to advance liver and biliary disease research that can be pursued by others with this common mission.